Open Journal of
Clinical & Medical
Case Reports

Volume 3 (2017)
Issue 15

ISSN 2379-1039

Management of hepatic epithelioid haemangioendothelioma: 5 year single-center experience and literature review

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Abstract

Introduction: Hepatic epithelioid haemangioendothelioma (HEHE) is a rare vascular tumor of unknown etiology, with no generally accepted therapeutic strategy because of its rarity and the variable natural course between hemangioma and angiosarcoma.

Aim: To report our experience and long-term outcomes after multimodal management therapy of this type of tumor.

Methods: An observational retrospective study was performed containing six patients with HEHE treated in our institution, a tertiary referral center, from 2010 to 2015. Demographic, preoperative, surgical and outcome variables were collected. A survival analysis and a review of the current literature related different treatment options were performed.

Results: All patients were women who were referred for evaluation for hepatic tumors that were discovered during a routine abdominal ultrasound. The first patient had recurrent disease 7 years after an initial successful liver resection for HEHE and was started on systemic therapy with a good response. The second patient who had a history of high doses of oral contraceptives, was diagnosed with unresectable HEHE, developed partial spontaneous regression and is alive and well more than 6 years after the diagnosis. Two other women, who had unresectable disease at the time of the diagnosis, one with no extrahepatic metastases, and the other with limited bone involvement were the first patients in Romania to receive a liver transplant for this indication. Our fifth patient had extensive disease at the time of diagnosis involving both liver and lung that progressed rapidly despite systemic chemotherapy with a fatal outcome. The last patient with extended liver disease was operated but developed early recurrence. In all six patients the diagnosis was established by immunohistochemical analysis of liver biopsy specimens.

Conclusion: Diagnosis of HEHE in young or middle aged women who present with asymptomatic usually bilobar liver masses should be considered. Liver transplantation is a valuable treatment even in cases of extrahepatic localisation of the disease. Given the low frequency of the disease, its variable natural history and the lack of current guidelines for management, therapeutic interventions should be decided on a case-by-case analysis.

Keywords

liver mass; primary hepatic epithelioid haemangioendothelioma; liver transplant

Introduction

Epithelioid hemangioendothelioma is a rare vascular tumor showing intermediate behavior, which can arise from soft tissue, bone, skin and various parenchymatous organs including liver, spleen, and lungs [1,2,3]. Hepatic epithelioid haemangioendothelioma (HEHE) usually affects adult women, and its malignant potential ranges between benign hemangioma and malignant hemangioendotheliosarcoma with rapid progression and a very poor prognosis [4,5].

The management of this uncommon hepatic tumor remains debated especially for bilobar liver disease and in the case of extrahepatic involvement. Several different surgical and non-surgical treatment options have been proposed including liver resection, liver transplantation, ablation therapy, immunotherapy, chemotherapy, radiotherapy, and hormone therapy but, due to the rarity of the disease and due to the natural history of HEHE, the best effective curative strategy is currently difficult to define [4,6].

Here we report our experience of six cases that were diagnosed and treated in our clinic: one patient with recurrent disease 7 years after an initial successful liver resection for HEHE with a good response to systemic therapy, another patient who had a history of high doses of oral contraceptives, was diagnosed with unresectable HEHE, developed partial spontaneous regression more than 10 years after the diagnosis, two patients with unresectable HEHE that received a liver transplant, a fifth case with rapidly progressive disease involving the liver and lungs with fatal outcome 3 months after symptoms onset, and the last patient who had a resection for multiple focal liver disease but developed early recurrence. A literature review of clinical features, diagnosis, and management is also provided.

Materials & Methods

All patients diagnosed with HEHE and treated at our institution, a tertiary referral center, between 2010 and 2015 were included in this observational retrospective analysis. Demographic (age, gender, risk factors); preoperative, initial presentation, location and volume of the tumors, method of diagnosis, tumor spread at diagnosis, and preoperative chemotherapy; surgical procedure performed; tumor characteristics, (histology, margins, and vascular invasions); and outcome (complications of treatment, recurrence and overall and disease-free survival) variables were collected.

Between 2010 and December 2015, six patients were diagnosed with HEHE at our institution. All patients were women with a median age of 40 years (range 25 to 57 years). The definition of HEHE was based on the criteria established by Ishak, Weiss and Dehner.

All six patients had hepatic epithelioid haemangioendothelioma (HEHE). In five patients, the primary symptom was right upper quadrant pain. Two patients had hepatomegaly, and one patient had signs of portal hypertension. All patients presented with multifocal tumour localisation, and 4 patients had extrahepatic lesions. Liver tests showed abnormal values in three patients with an increased alkaline phosphatase. All patients had normal serum levels of tumour markers and positive immunohistochemistry staining for endothelial markers.

A 57-year old asymptomatic female patient was initially admitted to our clinic in 2003 with multiple liver masses discovered at a routine abdominal ultrasound. A liver biopsy was performed and a diagnosis of multifocal HEHE was established. (Figure 1) There was no evidence of distant metastases and therefore a transverse hepatectomy (segments IVB, V, VI) and an atypical hepatectomy (segments III and VII) were performed. At that time she received 6 cycles of adjuvant chemotherapy with Cisplatin plus Doxorubicin The patient was lost to follow up for 7 years until 2010 when she returned with three liver masses 2 cm, 1.5 cm and 2.5 cm in diameter in both lobes and multiple lung metastases. The liver biopsy confirmed a recurrent HEHE. Palliative chemotherapy with Cisplatin and Doxorubicin (3 cycles) was administered followed by Capecitabine 1000 mg/m^2 bid p.o. day 1-14 (every 21 days) stopped after 5 months because of grade 3 Hand-foot syndrome. Evaluation of tumor response by serial CT scans showed stable disease for 15 months with a minimal decrease in the size of lung metastases but with no major changes in size of the liver tumors. The patient was lost from follow-up but she is alive (12 years after initial diagnosis).

The second patient a 25-year-old female with no relevant medical history presented to our department with fatigue and weight loss, 5 Kg in the last two months before admission. She admits taking oral contraceptives in high doses in the last 4 years. Clinical exam revealed an underweight patient with normal findings on the physical exam. She had low replicative chronic hepatitis B, (HBV DNA: 460 UI/ml), no cytolysis and tumor markers were within normal range. Abdominal ultrasound showed multiple confluent lesions in both liver lobes, which were suggestive for tumors of vascular origin on CT and MRI scan and no extrahepatic spreading was detected. (Figure 2) A liver biopsy was performed and the histological and immunohistochemistry examination, which showed reactivity for endothelial markers (CD34, factor VIII-related antigen, vimentin) was suggestive of HEHE. (Figure 3) The patient was listed for liver transplant and follow up examinations showed partial spontaneous regression with more 50% reduction in tumor volume, at two years after the initial diagnosis. The patient is doing well more than five years later, with all subsequent imaging evaluations showing stable disease.

The next two patients 42 and 56-year old females with no relevant medical history presented to our clinic for investigations being diagnosed with multiple space-occupying liver lesions during a routine abdominal ultrasound. In both cases physical examination showed an enlarged liver with no splenomegaly, no peripheral lymphadenopathy and laboratory results were within normal range except a moderate increase of alkaline phosphatase and an elevated CRP. Tumor markers were all within normal range and hepatitis viral markers were negative. Abdominal imaging examination showed in both patients bilobar liver masses ranging from 40 to 85 mm, suggestive for secondary lesions, without intra-abdominal lymphadenopathy. (Figure 4A, 4B, 4C; Figure 5) Upper endoscopy, colonoscopy and mammography were normal.

US-guided liver biopsies were performed and microscopy showed pleomorphic neoplastic cells with rounded nuclei and scant cytoplasm occasionally arranged in vascular channels, and several intracytoplasmic vacuoles containing erythrocytes. Immunohistochemistry of tumor cells showed reactivity for CD68, CD34, cytokeratin 18, vimentine and was negative for cytokeratine 7, cytokeratin 8, and CEA. The fusion genes weren't examined. A diagnosis of HEHE was made based on these findings (Figure 6; Figure 7).

Both patients were evaluated for liver transplantation. A thoracic CT and a FDG-PET scan showed no extrahepatic tumor spread in the first patient but showed limited bone spreading in the 56 year old patient, so they were both listed for transplant. Three and eleven months respectively after their initial diagnosis both patients received an orthotopic liver transplant, being the only patients with HEHE transplanted in Romania. The patients are well being with no tumor recurrence after transplant (disease free-survival time after liver transplantation 36 months in the first case and 28 months in the second).

The fifth patient, a 25-year-old female with no relevant medical history presented to our department with dyspnea, nausea, cough, weight loss, pain the right upper abdominal quadrant. She has given birth to a healthy child 5 years ago and admits taking oral contraceptives in the last 4 years. Clinical exam revealed a pale patient with minimal effort dyspnea, an enlarged painful liver 5 cm under the costal arch, dullness on percussion in the middle and lower half of the thoracic wall and pain in lower back and right leg. Mild anicteric cholestasis and cytolysis were present and tumor markers were within normal range. Chest computed tomography (CT) showed multiple mediastinal adenopathies, several metastatic nodules with diameters ranging from 7 to 23 mm in both lungs and a large right side pleural effusion. (Figure 8A) Abdominal CT confirmed hepatomegaly and reveled multiple tumor masses in both liver lobes (largest tumor 145/125/200 mm) and multiple lytic bone lesions of the lumbar vertebrae and sacral bones. (Figure 8B) A liver biopsy was performed and the histological and immunohistochemistry examination was suggestive of HEHE. (Figure 9) The patient was treated with Paclitaxel 80 mg/m2 weekly and bisphosphonates for bone metastasis but she died three months later.

A 39-year old female, was diagnosed in another unit with multiple bilobar focal liver lesions (9 nodules ranging from 5 cm to 1.5 cm) for which she underwent liver biopsy that established the diagnosis of HEHE. (Figure 10; Figure 11) FDG-PET scan revealed no extrahepatic disease. Consequently, ultrasound-guided multiple non-anatomical liver resections were performed for 13 nodules (9 known preoperatively, and 4 newly found at intraoperative ultrasound). Local recurrence occurred at 8 months after surgery (2 small new liver nodules distant to the prior resections), despite the fact that all specimens had histologically negative margins. The patient is scheduled for re-resection after a short follow-up to prove stable disease.

Discussion

In 1982 Weiss and Enzinger proposed the term epithelioid hemangioendothelioma to describe a group of soft tissue vascular tumors of endothelial origin with the liver being the most frequently site, followed by bone skin and other parenchymatous organs [1-6]. The etiology and pathogenic factors of this tumor remain unknown but previous use of oral contraceptives, exposure to vinyl chloride or major hepatic trauma had been reported [4].

HEHE was first reported in 1984 by Ishak et al in a series of 32 cases, and develops mainly in adults, with a higher prevalence in women (woman: man ratio, 1.6-2.0: 1) [1]. The clinical manifestation of HEHE may vary from an asymptomatic state (20% of patients) to hepatic failure. The most frequent symptoms are upper abdominal pain, weakness, impaired general condition and jaundice. About 10% of patients present with pulmonary symptoms [6,7]. Hepatosplenomegaly and weight loss are the most frequent clinical signs. Portal hypertension may be caused by vascular compression or infiltration. Anicteric cholestasis and cytolysis are present in 60% and 40% of patients. Serum tumor markers are

normal in the absence of accompanying liver disease [6].

Mildly elevated ALP and GGT were the most common types of abnormal liver function tests in our series with almost the same incidence as reported in the literature. Of note, liver function tests may be within the normal range in the early stage of the disease, however, with disease progression, HEHE may involve more liver parenchyma and result in elevated liver enzymes in the later stages of the disease.

Imaging identifies an early peripheral and nodular, usually bilobar, type (peripheral pattern) and a later confluent type (diffuse pattern) with eventual invasion of the greater vessels [4] [6]. Calcifications are present in 20% of tumors. A typical imaging finding is the "capsular retraction sign" which in correlation with the "halo sign" after intravenous administration of contrast could improve the diagnostic accuracy for this type of tumor [4]. The presence of capsular retraction in subcapsular hepatic tumors, along with a target like appearance of the tumors on contrast-enhanced CT and MR images, is suggestive but not necessarily indicative of HEH [19]. Such signs can be found in peripheral cholangiocarcinomas, confluent foci of hepatic fibrosis, treated primary or metastatic hepatocellular carcinomas, and large atypical cavernous hemangioma. Complete assessment of these patients is mandatory to exclude other, especially thoracic and bone disease localization. FDG-PET imaging plays a role in the staging of the disease and in early detection of recurrent disease.

Macroscopically, HEHE appears as multifocal fibrous masses and microscopically epithelioid cells are arranged in strands, cords and nests that spread within sinusoids. The endothelial origin of HEHE explains positive immunohistochemistry (IHC) for FVIII-related antigen and endothelial markers CD31, CD34, vimentin and podoplanin [8].

The clinical course of HEHE can be extremely variable from prolonged spontaneous survival (up to 28 years!) [5] to rapidly progressing disease with fatal outcome, as our series demonstrate. In a review of 60 cases of HEHE available for analysis of follow-up data after diagnosis, Makhlouf et al reported a median survival period of 51 months ranging from 4 months to 336 months after diagnosis [6].

There are no standard therapeutic strategies for HEHE until now, the management of the disease depending on the presence of dissemination at the time of diagnosis. Treatment options include liver resection, liver transplant with or without embolization for bridging, thermoablation, chemotherapy, radiotherapy or hormonal therapy and even follow up without therapy. Patients having tumors restricted to the liver are good candidates for surgery, either local resection or liver transplant. A standard systemic treatment has not been established for advanced tumors. A small number of single case reports of HEHE patients treated with cytotoxic chemotherapy have been published [9] [10]. The most frequently used agents are doxorubicin, fluorouracil and cyclophosphamide however, the results have been far from ideal and HEHE is considered a chemoresistant tumor [10]. Pegilated liposomal doxorubicin administered i.v. with long circulation time ends up reaching a high concentration in reticuloendothelial cells and can be used successfully in a low dose maintenance regimen [9]. Until now, there are no other cases reported in literature in which Capecitabine was used, as was the case in our first patient who show stable disease 12 months after Capecitabine was started. Recent data suggests that antivascular endothelial growth factor (VEGF) is an option for decreasing tumor volume or as an adjuvant after liver transplant. The anti VEGF monoclonal antibodies (Bevacizumab, Ranibizumab) or inhibitors of tyrosine kinases associated with VEGFR-2, VEGFR-3 and PDGF-β (sunitinib, sorafenib).

Liver transplantation for HEHE, long time a subject of controversy, has been clearly defined as a good therapeutic option by Lerut et al. in review of 59 transplanted patients in Europe who had a five- and 10-year post-transplant survival rate of 83% and 74%, respectively even in the presence of lymph node involvement or limited extrahepatic disease because both factors did not significantly affect survival when appropriate multimodal treatment were employed [11] [12] [13]. Nudo et al. in a Canadian study of 11 transplanted patients for HEHE reported a 5-year survival rate of 82% with a recurrence rate of 36.4% [14]. Our patients are the first two cases of liver transplant for HEHE in the Romanian Transplant Program and they show no recurrent disease after 2- and 1 year follow up period, respectively.

Combined micro- and macrovascular invasion (present in half of the patients) was the only parameter, which significantly influenced outcome after LT [12]. None of our transplanted patients had vascular invasion.

Several case reports have described a rapid course and fatal outcome after onset of symptoms in HEHE similar to our fourth case. Terg et al. reported a 28-year-old man with abdominal pain and cholestasis who died within 6 months of symptom onset [15] and Komatsu et al. described a case of a 46-year old woman who developed rapidly progressive respiratory and hepatic failure and disseminated intravascular coagulation and died 4 months after initial presentation [16]. The final clinical outcomes may include liver failure caused by loss of parenchyma or portal hypertension (tumor cells invading and occluding presinusoidal and postsinusoidal space). The fourth reported case in our series has shown an accelerated progression and died within 3 months from the onset of symptoms, which is considered a rare clinical course in HEHE.

On the other hand, there are several case reports which describe patients with multiple lesions which have undergone regression (one case with complete spontaneous remission) [17] even without any specific therapy as shown in our case no. 2.

Theoretically, resection is the first choice for curative treatment of HEHE but in the majority of patients, an oncologic resection is impossible because of the multicentricity of the lesions or anatomic difficulties. Although clinical experience with tumor resection is considered satisfactory by many, there some authors that hesitate to perform liver resections for patients with apparently resectable disease due to disappointing results [7, 18]. Based on their experience, a possible explanation for the aggressive tumor behavior after resection may be tumor cell reactivity to the hepatotrophic growth factors that promote hepatic regeneration [18]. We had two patients with liver resection for multicentic tumors which developed recurrence despite the fact that all specimens from both patients had an R0 resection margin, but we did not find an aggressive tumoral behavior after resection.

In conclusion we present our experience with six cases that emphasize that clinical presentation, course, prognosis and therapy of HEHE can vary widely. Liver transplantation is a valuable treatment even in cases of extrahepatic localisation of the disease. Given the low frequency of the disease, its variable natural history and the lack of current guidelines for management, therapeutic interventions should be decided on a case-by-case analysis.

Table

Table 1: Clinical data of patients diagnosed with HEHE

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age (yr)/ gender	57/F	25/F	42/F	56/F	25/F	39/F
Symptoms and signs	RUQ pain Hepatomegaly liver resection 7 years before	fatigue weight loss	RUQ pain Hepatomegaly	RUQ pain Hepatomegaly	RUQ pain Hepatomegaly Dyspnea GI intolerance Anaemia	RUQ pain
Liver lesions	3	> 5	3	4	2	4
Sites of metastases	lung	none	none	none	lung	lung
Treatment after diagnosis	CDDP, Doxorubicine, changed to capecitabine due to toxicity	none	none before liver transplant	none before liver transplant	Paclitaxel biphosphonates	Radical surgery
Delay diagnosis - LT (months)	-	-	3	11	-	-
Imunosupression after transplant	-	-	sirolimus	sirolimus	-	-
Reccurence	Yes		No	No	-	Yes
Survival	alive 12 years	alive 10 years	alive 36 months	alive 28 months	dead after 3 months	alive 12 months

Abbreviations: RUQ-right upper quadrant

Figures

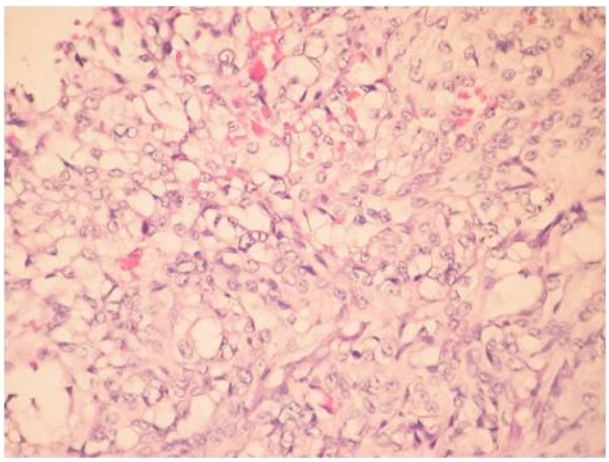

Figure 1: Pathological findings from liver biopsy: Microscopy showing slightly pleomorphic neoplastic cells with rounded nuclei and scant cytoplasm occasionally arranged in vascular channels. The cytoplasm included many vacuoles containing erythrocytes (Hematoxylin and Eosin staining; ×400) (Patient no.1)

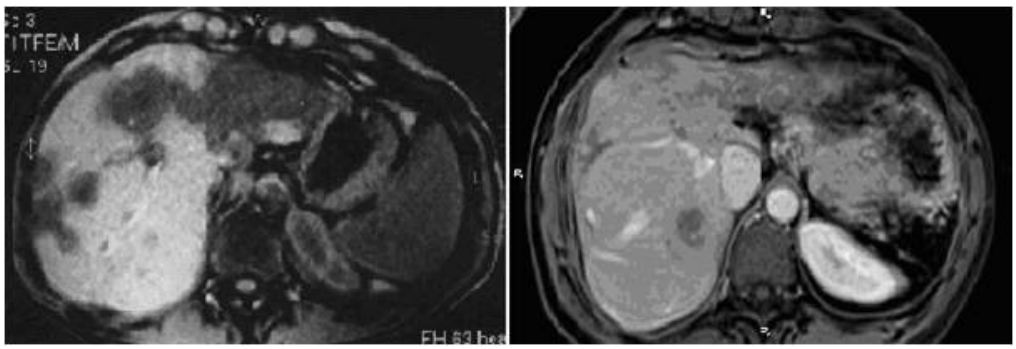

Figure 2: A) several lesions hypointense relative to normal liver parenchyma on unenhanced T1-weighted images and with heterogeneously increased signal intensity on T2 images. (left liver lobe is completely occupied by a large lesion) The lesions demonstrate a target-type enhancement pattern after administration of a gadolinium-based contrast agent; with observation of a thin peripheral hypointense rim (Patient no.2) B) partial tumor regression 10 years after initial diagnosis.

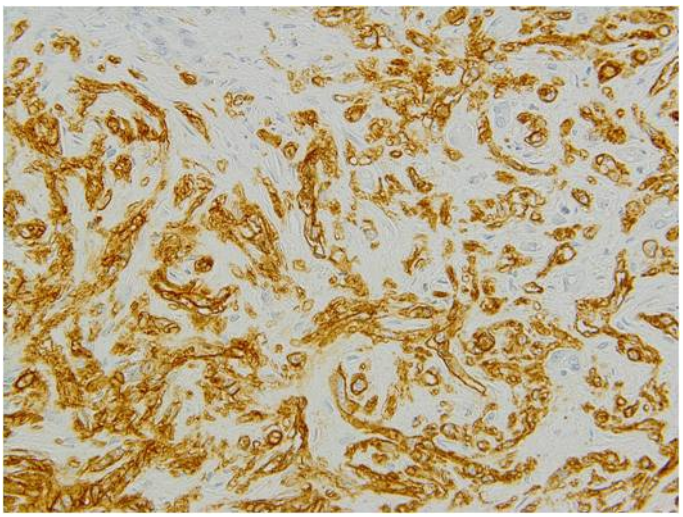

Figure 3: Pathological findings from liver biopsy: Tumor cells immunostained with antibody to CD34 (×400) (Patient no.2)

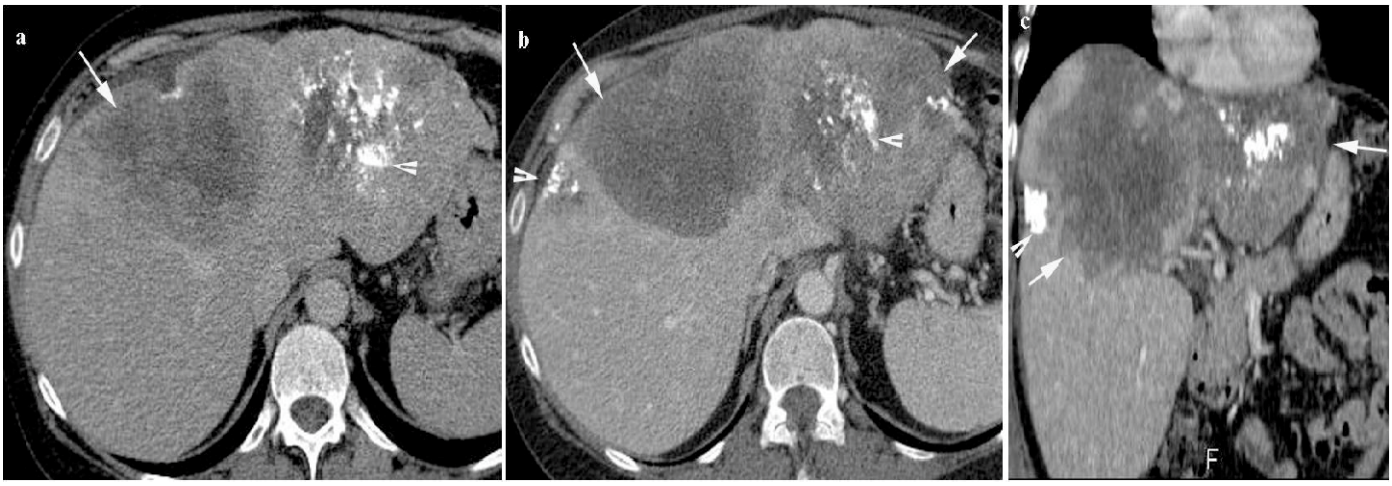

Figure 4 A,B,C: Diffuse left liver mass: enhanced CT (a,b,c) shows a large and diffuse areas of low attenuation (white arrows), with intratumoral calcifications (arrowhead). The vascularity of the diffuse mass is low to moderate, with a predominant peripheral tumor enhancement surrounding the central low-attenuation fibrous core. Retraction of the overlying capsule is due to lesion-related fibrosis (transparent arrow). (Patient no.3)

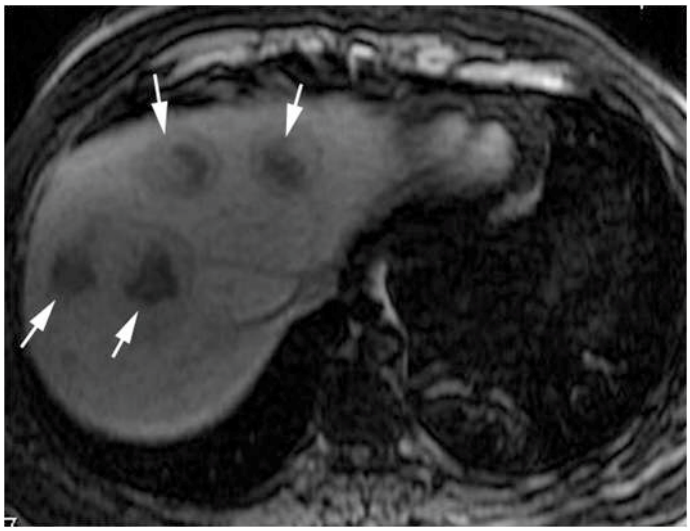

Figure 5: Multiple bilateral, solid, hepatic lesions, hypointense on T1-weighted MRI with central necrosis (Patient no. 4)

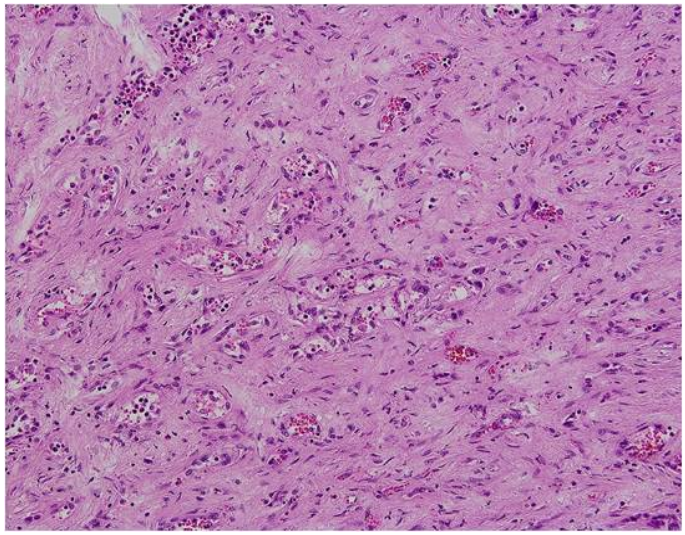

Figure 6: Pathological findings from liver biopsy: Microscopy showing pleomorphic neoplastic cells with rounded nuclei and scant cytoplasm Hematoxylin and Eosin staining; ×200) (Patient no.3)

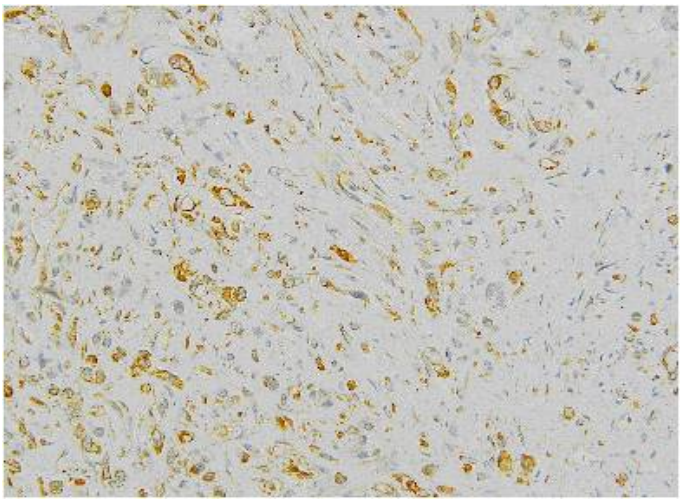

Figure 7: Pathological findings from liver biopsy: Tumor cells immunostained with antibody to vimentin (×400) (Patient no.4)

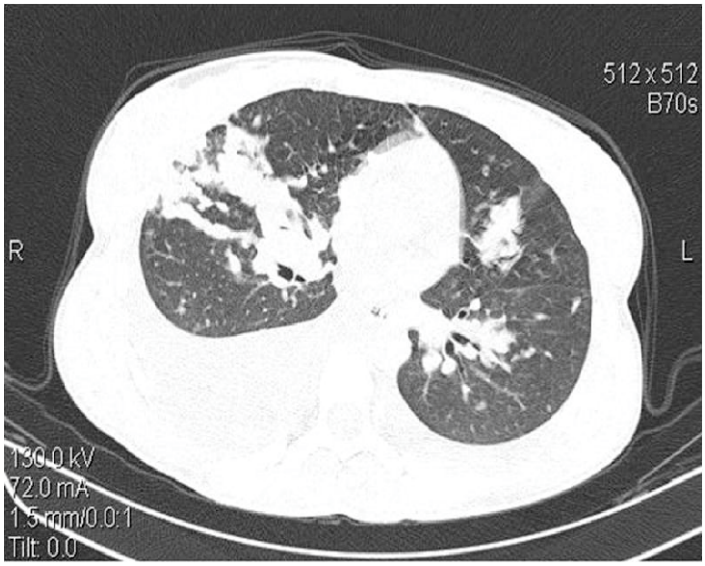

Figure 8A: Thoracic CT scan using lung window showing bilateral lung areas of consolidations and a large right side pleural effusion (Patient no. 5)

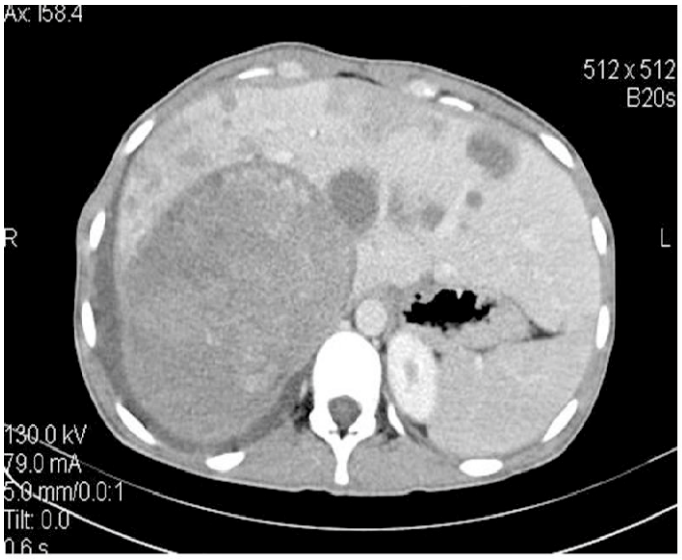

Figure 8B: Abdominal CT scan shows multiple bilateral hypoattenuating, hypoenhancing liver tumors (the largest lesion 145/125/200 mm in diameter) (Patient no. 5)

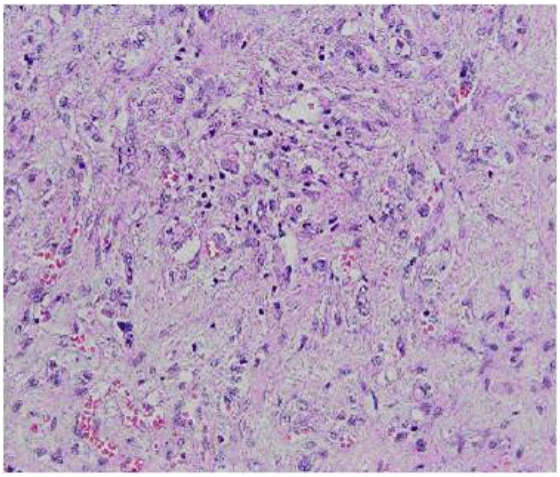

Figure 9: Pathological findings from liver biopsy: Microscopy showing epithelioid tumor cells occasionally arranged in small nests, with abundant eosinophilic cytoplasm and moderate nuclear pleiomorphism (Hematoxylin and Eosin staining; ×400) (Patient no.5)

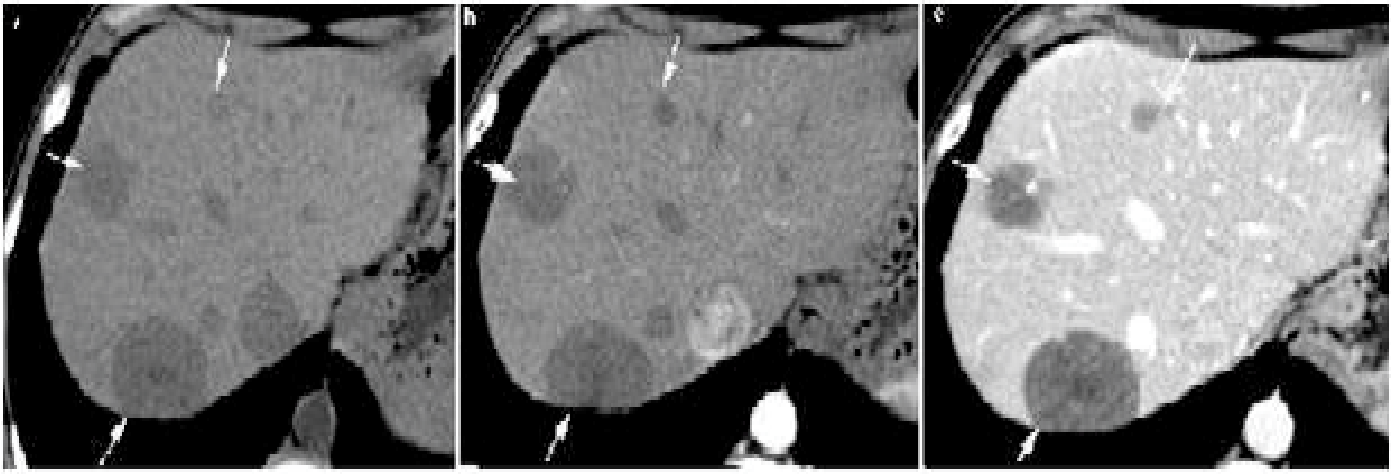

Figure 10: Unenhanced CT (a): multiple, round-oval lesions of low attenuation with a peripheral distribution. Contrast-enhanced CT in arterial (b) and venous (c) phase delineate a layered appearance of the largest nodule located into the VII liver segment (arrow); note also the retraction of the overlying capsule (arrowhead) (Patient no.6)

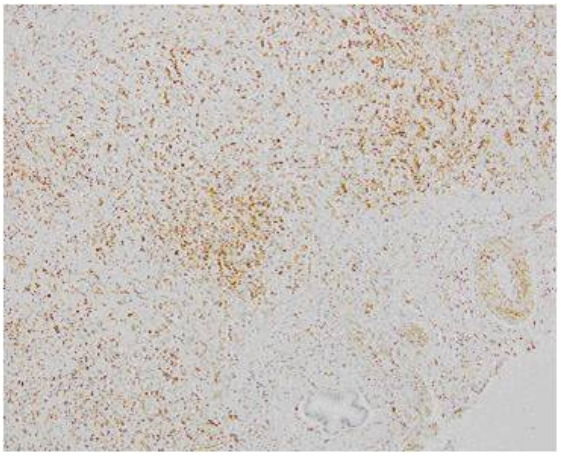

Figure 11: Pathological findings from liver biopsy: Tumor cells immunostained with antibody to vimentin (×100) (Patient no.6)

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Manuscript Information: Received: March 05, 2017; Accepted: July 26, 2017; Published: July 30, 2017

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Citation: Cerban R, Croitoru A, Becheanu G, Popescu I, Lupescu, Botea F, Gheorghe L, et al. Management of hepatic epithelioid haemangioendothelioma: 5 year single-center experience and literature review. Open J Clin Med Case Rep. 2017; 1294.

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